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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/197,056 11/20/98 RUSSELL

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EXAMINER

WILSON, M

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 08/17/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/197,056

Applicant(s)
Russell et al.

Examiner
Wilson, Michael C.

Group Art Unit
1633



☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-18 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-18 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Claims 1-18 are under consideration in the instant application.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 14-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim reads on cells which are within a human host which is non-statutory subject matter. The addition of the word "isolated" before the word "cell" would overcome this rejection.

Claim Objections

2. Claim 18 is objected to because of the following informalities: the use of parentheses is improper when referring to the analogues of tetracycline. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating the expression of a nucleic acid sequence encoding an immunogenic peptide *in vitro* comprising a) transfecting a cell with a nucleic acid

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sequence encoding an immunogenic peptide operably linked to a tetracycline regulatable system and b) regulating the expression of the sequence by administering tetracycline which results in an alteration in expression of the nucleic acid sequence, does not reasonably provide enablement for a method of regulating the expression of a nucleic acid sequence using a non-tetracycline regulatable system, or regulating the nucleic acid *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

For clarification, the examiner considers an immunogenic polypeptide as any protein which induces an immune response such as GM-CSF or a chimeric T-cell receptor as disclosed in the specification (page 7, line 24).

Therapy

Claims 11-12 are directed toward delivering cells comprising DNA encoding a polypeptide which exerts a therapeutic effect in the mammal, specifically, an anti-tumor effect (claim 12). While applicants may deliver a nucleic acid sequence encoding an immunogenic peptide, the specification does not enable obtaining a therapeutic effect in the mammal. At the time of filing, it was unpredictable whether the administration of DNA encoding immunogenic polypeptides against tumors would have a therapeutic result. In Ross et al. (Sept. 10, 1996, Human Gene Therapy, Vol. 7, page 1781-1790) the *ex vivo* approach used to treat tumors resulted in only 1 melanoma patient **who might** be considered to have had a clinical response, however it may have occurred spontaneously because melanoma is known to regress spontaneously (page 1786,

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column 1, paragraph 2). Ross et al conclude it is unpredictable whether a therapeutic result can be obtained using *ex vivo* gene therapy (page 1786, column 1, paragraph 2). Verma et al. (Sept. 18, 1997, Nature, Vol. 389, pages 239-242) states the *in vivo* approach of gene therapy is unpredictable because of an inability to deliver genes efficiently and to obtain sustained expression (see page 239, 3rd column, line 10). "Although more than 200 clinical [gene therapy] trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (page 239, column 1, line 16). Thus, the state of the art of gene therapy is such that there is a lack of correlation between expression of a gene product and therapeutic effect using gene therapy methods.

From this analysis of the state of the art at the time of filing, the artisan would need to rely on the specification for guidance in determining effective dosages and routes of administration to achieve a therapeutic or prophylactic effect using *in vivo* or *ex vivo* gene therapy methods. However, the specification demonstrates constructing regulatable vectors encoding GM-CSF and a chimeric T-cell receptor. Applicants also demonstrate the chimeric T-cell receptor is capable of inducing IL-2 production in cells *in vitro* (page 29). Applicants do not provide the proper route of administration, vector, promoter or dosage that provides efficient gene delivery or the level of expression of GM-CSF or chimeric TCR required to obtain a therapeutic or anti-tumor effect. Nor do applicants demonstrate obtaining a therapeutic or anti-tumor effect using the method of the instant invention. Alvarez-Vallina et al. (March 1, 1999, Human Gene Therapy, Vol. 10, pages 559-563) teach that activation in the Jurkat model of expressing chimeric TCR parallels the

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activation of normal T-cells but that analysis of T-cell response over a period of time is required to determine the applicability of cells expressing chimeric TCR (page 562, column 2, line 1). The teachings in the art do not provide adequate guidance indicating cells expressing chimeric TCR have any therapeutic or anti-tumor effect as claimed. Without such guidance, it would require one of skill undue experimentation to determine the parameters required to obtain a therapeutic or anti-tumor effect.

Regulatory promoter systems

Miller et al. (May 1, 1997, Human Gene Therapy, Vol. 8, pages 803-815) teach the gene regulation system that can be applied to gene therapy in humans is yet unknown (page 809, column 2, line 42). Applicants do not demonstrate regulating any genes in humans or in any art recognized *in vivo* model. Without such guidance, the specification does not enable regulating the expression of a transgene in a mammal as claimed. In particular, the specification does not enable regulating the expression of a polypeptide by altering the concentration of regulatory drug after the cell has been administered as encompassed by claim 1. The specification does not teach dosage, routes of administration or methods of targeting cells transfected with the polypeptide such that expression can be regulated after the cells have been introduced.

Claims 1-17 are not fully enabled because the specification does not enable using any regulatory drug system other than the tetracycline regulatable system (TRS). The specification does not enable using glucocorticoid steroids, sex hormone steroids, LPS or IPTG (claim 10) because the specification does not teach the promoters that are controlled by these regulatory

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drugs (page 10, line 9). These promoters are considered to be essential to the practice of the invention for its claimed scope and have not been taught in the instant specification. In addition, the specification does not enable regulating gene expression using any drug-regulatable promoter as recited in parent claim 1 using any of the drugs listed in claim 10. For example, sex hormone steroids do not regulate a nucleic acid with a tetracycline promoter. The specification does not enable regulating a gene sequence operatively linked to a tetracycline promoter using any tetracycline system other than the ones exemplified in the specification because the tetracycline system used is specific to the cell line as stated above by Miller et al. and because it is unpredictable what promoter system is used for a specific gene therapy protocol to obtain a therapeutic effect. Finally, Miller et al. teach attempts to produce regulatable systems for gene therapy based on inducible cellular promoters are fundamentally flawed because 1) the effects of the inducer must induce the endogenous promoter and the transgene promoter and 2) interference from endogenous activators may prevent expression (page 808, column 1, 2nd full paragraph). Claims 1-9 and 11-17 as written are not limited to non-cellular promoter systems such as tetracycline. The specification does not teach using any inducible cellular promoter. Thus, the specification does not enable the breadth of claims 1-17.

Claims 10 is directed toward various regulatable systems including the tetracycline system. Miller et al. teach that it is unpredictable what cells the tetracycline system may be applied (page 809, column 2, 2nd full paragraph). Applicants demonstrate transfecting T-cells with a chimeric TCR under the control of a tetracycline system and controlling expression *in vitro* (page 29) but

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do not correlate the results obtained to other cell lines such that any cell line is enabled. Thus, if applicants intend to claim using the tetracycline regulatory system, the claims should be limited to cells enabled in the specification. Without adequate guidance as to which cells can be used to express proteins using the tetracycline regulatory system, it would require one of skill undue experimentation to determine which cells can be used with the tetracycline regulatory system.

Other

Claim 1 as written encompasses cells naturally comprising the nucleic acid sequence of interest. The specification does not enabled obtaining cells naturally expressing a nucleic acid sequence encoding an immunogenic protein operably linked to drug-regulatable promoter by any means other than by transfection. It is not clear that any naturally occurring cells with a drug-regulatable promoter exist or how to obtain such cell other than by transfection.

Claims 4-6 are directed toward a method of regulating gene expression wherein the mammal has made an immune response to the immunogenic peptide in a mammal. The claims as written do not clearly state that the immune response is a result of the expression of the immunogenic polypeptide. The mammal may have made an immune response to the immunogenic polypeptide before administration of the nucleic acid sequence which is not taught or suggested in the specification. The specification teaches that the immunogenic polypeptide is expressed to detectable levels and recognized by the immune system. This, in turn, causes an immune response and is required to obtain circulating antibodies or immunocompetent memory cells (claims 5 and 6) against the polypeptide. The claims are not enabled as written because the claims do not

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provide a nexus between a method of regulating a gene which results in an immune response. If applicants intend to claim a method of inducing an immune response in a mammal, the preamble should reflect the substance of the claim. In particular, the specification does not enable obtaining memory cells as claimed (claim 6). The specification does not provide an assay to determine whether cells obtained are memory cells or provide any guidance or demonstration how to obtain memory cells. Applicants demonstrate constructing expression vectors encoding GM-CSF. It is not clear how to obtain memory cell response by administering GM-CSF. It would require one of skill undue experimentation to obtain memory cells using the instant invention.

Administration of cells which have been regulated *in vitro* to express different levels of protein (claims 7-9) is not a method of regulating the expression of a nucleic acid sequence in a mammal as claimed (see 112/2nd rejection) because the “regulating” does not take place in the mammal. The specification does not enable regulating the expression of a protein in a mammal by regulating the gene while it is within the mammal. If applicants wish to claim administering cells which have been regulated *in vitro*, the preamble should not recite “regulating the expression in a mammal of a nucleic acid sequence” The preamble should reflect the substance of the claim to be enabled.

The specification does not enable the term “delay interval” (claim 7) because the term is not defined in the specification and does not have a art recognized meaning. The method requires a step of waiting for maximum gene expression, but the claim as written does not include such a step. The specification does not teach the “delay interval” that provides maximal expression.

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Claim 13 is directed toward a nucleic acid sequence encoding a replicable viral genome or a viral vector. The vector used is considered essential to the instant invention. The specification does provide any guidance on viral vectors or replicable viral genome which can be used in the instant invention. Therefore, the specification does not enable using viral genome or viral vectors as claimed.

Claims 14 -16 are not enabled because the specification does not teach transforming the cells within a host which is encompassed by the claim. Addition of the term "isolated" before the word "cell" on line 1 would overcome this rejection. Claim 18 encompasses transforming cells within a mammal. As stated above, the state of the art at the time of filing was such that obtaining expression of a polypeptide by gene therapy was unpredictable. The specification does not teach the dosage, route of delivery, vector and promotor used to direct transfection to leukocytes as claimed.

Therefore, in view of the lack of guidance in the specification regarding how to regulate gene expression *in vivo*, how to obtain a therapeutic effect, the level of expression of a gene required to obtain a therapeutic effect, the lack of correlation between *in vitro* gene regulation and *in vivo* gene regulation, the level of expression obtained *in vitro* and the level of expression required *in vivo* to obtain a therapeutic effect, the unpredictability in gene therapy, gene regulation in gene therapy and the types of cells to use with tetracycline regulatory systems, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant

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invention would not have known how to make and/or use the claimed invention with a reasonable expectation of success.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the phrase "in a mammal of a nucleic acid sequence" is indefinite because the mammal is not "of a nucleic acid sequence".

Claims 4-6 are indefinite because the preamble and the substance of the claims do not provide a nexus between the two. The claims are directed to a method of regulating gene expression, but the substance of the claim is directed toward a method of inducing an immune response. Such a claim is confusing.

In claims 7-9, the phrase "delay interval" is indefinite because the phrase is not defined in the specification and does not have a art recognized meaning.

Claim 8 is indefinite because the phrase "substantially free" is not defined in the specification and may have various meanings in the art. The same argument applies to the phrase "substantial absence" in claim 9. It is unclear whether applicants intend "substantial(ly)" to mean 75%, 50% or some other percentage. The phrase "mammal of the regulatory drug" is indefinite because the mammal is not "of the regulatory drug".

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Claim 16 is indefinite because the phrase "plurality of a cell of claim 14" is unclear. A plurality cannot be a cell as claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Taichman et al. (1993, Biotechniques, Vol. 14, pages 180 and 182).

Taichman et al. teach producing a plasmid encoding a tyrosine kinase operatively linked to an inducible MT-I promoter and transfecting T-cells with the plasmid (page 180, column 2, line 13). The expression of the transgene is controlled by altering the concentration of zinc in the media (page 180, column 1, second to last sentence). Since all proteins are immunogenic, the tyrosine kinase protein is an immunogenic polypeptide as claimed. The media taught by Taichman et al. is considered equivalent to the physiologically acceptable diluent claimed.

Conclusion

No claim is allowed.

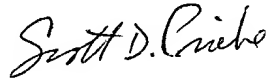
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

A handwritten signature in cursive script, reading "Scott D. Pribe".

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER